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08/319,357 10/06/94 SCHMITT-WILLICH

H SCH1412

EXAMINER

CHAPMAN, L

ART UNIT

PAPER NUMBER

12M2/1130
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1208

DATE MAILED:

11/30/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

3/5/95
perfor
9/16/95

This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

<input checked="" type="checkbox"/> Notice of References Cited by Examiner, PTO-892.	<input checked="" type="checkbox"/> Responsive to communication filed on <u>9/16/95</u>	<input checked="" type="checkbox"/> This action is made final.
<input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449.		
<input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474.		

Part II SUMMARY OF ACTION

1. Claims 2-9, 11, 13, 14, 16, 18-26, 29, 30, 32-43 are pending in the application.
Of the above, claims 3, 4, 7, 15, 19, 24-26, 29, 41-43 are withdrawn from consideration.
2. Claims 1, 10, 12, 15, 17, 27, 28, 31, 33-35 have been cancelled.
3. Claims _____ are allowed.
4. Claims 2, 5, 6, 8, 9, 11, 13, 14, 16, 20-23, 30, 32-36-40 are rejected.
5. Claims _____ are objected to.
6. Claims _____ are subject to restriction or election requirement.
7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. Formal drawings are required in response to this Office action.
9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been approved by the examiner; disapproved by the examiner (see explanation).
11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).
12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.
13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. Other

EXAMINER'S ACTION

1. Applicant's amendments filed 9/1/95 and 9/19/95 have been entered.
2. Applicant is required to make an election of species with regard to the compound to be examined. The claims of the present application contain a multitude of species. An election of species will require the applicant to elect a specific ligand and to further specify the various substituents placed on the elected ligand. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

The claims as presented contain such a vast multitude of "possibilities and permutations" that it is not possible to identify each and every species encompassed in the claims. Accordingly, to facilitate election, applicant is required to elect a single specific compound including the structure and upon such election the Examiner will review the claims and indicate (a) which compounds are so similar thereto as to be a part of the elected matter and, (b), by such indication (i.e. by exclusion) which compounds are drawn to non-elected matter.

It is considered that the "Markush" type claims encompassing such species are directed to multiple "independent and distinct inventions" since the species encompass compounds that are so unrelated and diverse that a prior art reference anticipating the claims with respect to one of the species will not render the claims obvious under 35 U.S.C. 103 with respect to any of the other species. Further, these claims encompass species that are considered to be independent since they are unconnected in operation; one does not require the others for ultimate use and the specification does not disclose a dependent relationship between them. Moreover, there are encompassed species that are considered to be distinct from the others on the basis of their properties. Also, it is an undue burden on the PTO to act on more than one invention in one case. Thus, this application contains species that are capable of supporting separate patents under 35 U.S.C. 121.

Accordingly, applicant is required to make a provisional election of a single independent and distinct species as noted supra, prior to the examinations of said claims

on the merits. This election will be given effect in the event that the "Markush" type claim(s) is (are) not found allowable, at which time the "Markush" type claim(s) directed solely to the elected species, with claims directed solely to the nonelected species being held withdrawn from further consideration. It should be noted that an election of species has been held to be tantamount to a requirement for restriction (In re Herrick, 1958 C.D. 1 and In re Joyce, 1958 C.D. 2) and enjoys the benefit of 35 U.S.C. 121.

3. Applicant's response must include a provisional election as noted *supra*, even though the requirement be traversed (37 CFR 1.143). Applicant is also advised that any traversal must be supported by specific argument(s) in order to perfect the right to petition in the event that the provisional requirement is given effect in the event noted *supra*. Applicant is also advised that arguments adequate to cause withdrawal of this requirement would warrant the ultimate conclusion that all species are patentably indistinct and a reference for one species would be considered a reference as to all species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 of the other invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

5. During a telephone conversation with Brion Heaney on 11/21/95 a provisional election was made with traverse to prosecute the species of Example 8(c) drawn to a gadolinium complex of the compound of Formula I where Z1 is H and Z2 is ethoxybenzyl. Affirmation of this election must be made by applicant in responding to this Office action. Claims 3, 4, 7, 18, 19, 24-26, 29, and 41-43 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected species.

6. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

7. Claims 2, 5, 6, 8, 9, 11, 13, 14, 16, 20-23, 30-32 and 36-40 are rejected under 35 U.S.C. § 103 as being unpatentable over Berg et al. (EP 299,795 or US 5,198,208) in view of Gries et al. (EP 263,059).

Berg et al. disclose DTPA derivatives "particularly useful for the preparations of diagnostic and therapeutic agents for magnetic resonance imaging, scintigraphy, ultrasound imaging, radiotherapy and heavy metal detoxification" (Abstract). The compounds of the Berg et al. invention contain pendant groups designated R1 which correspond to Applicant's Z substituents. Applicant's attention is drawn to the compounds listed on pages 19-22 and particularly to the structure IK on page 21. Berg et al. teach in the Abstract that R1 may be

a hydrogen atom, a hydroxyalkyl group, or an optionally hydroxylated alkoxy or alkyloxy group. On page 3, lines 20-30, Berg et al. discuss the metal ions to which the chelate can complex: "It is...particularly preferred that the number of the ion-forming groups X in the compounds of formula I be chosen to equal the valency of the metal species to be chelated by the compound of formula I. Thus, for example, where Gd(III) is to be chelated, the chelating agent of formula I preferably contains three ion-forming X groups...." Although Berg et al. disclose pendant alkyloxy substituents, they do not mention benzoxy substituents such that a benzyl group would be substituted for the alkyl portion of the pendant alkyloxy group.

Gries et al. disclose DTPA derivatives with pendant R1 groups which correspond to Applicant's Z substituents. Applicant's attention is directed to Formula I and the Abstract. Gries et al. teach in the Abstract the equivalence of alkyl groups, phenyl groups, and benzyl groups for the R1 substituent. Possible metals to which the ligands can complex are discussed on page 2 and include metals with atomic numbers of 21-29, 31, 32, 38, 39, 42-44, 49, and 57-83 which are useful for diagnostic purposes. Thus, since Gries et al. and Berg et al. both teach DTPA derivatives which complex with Gd and which are used for diagnosis, it would have been obvious to a person of ordinary skill in the art to utilize the teaching of Gries et al. to modify the invention of Berg et al. with an equivalent hydrocarbon group for the alkyl portion of the pendant alkyloxy group.

Furthermore, case precedent has held the equivalence of benzyl and alkyl groups: "Cyclo-lower-alkyl and phenyl radicals are so extremely common that we believe any chemist of ordinary competence would readily realize that said radicals might be substituted for...alkyl radicals" (*Ex parte Koster*, 136 USPQ 75). Thus, benzoxy and alkyloxy groups are believed to be equivalent structures to the ordinarily skilled organic chemist, and substituting one for the other would have been readily obvious to this artisan at the time of applicant's invention.

8. Applicants' arguments concerning the above rejections have been carefully considered but are not found persuasive.

With respect to the rejection over Berg et al. in view of Gries et al., applicants appear to have abandoned their intention to show unexpected results. Instead applicants argue that the examples of the references do not disclose what is currently being claimed. This suggestion, however, was never made by the examiner. Applicants further argue that Gries et al. does not provide motivation to extrapolate their equivalence teaching to other chelating complexes, but there is no such legal requirement that Gries et al. itself provide the motivation to combine their teaching with Berg et al. Applicants also argue that hindsight reconstruction has been invoked to make the rejection at issue and that a person of ordinary skill in the art would not be motivated to synthesize applicants' claimed compounds from the disclosures of the cited references. It is the examiner's position that one of ordinary skill in the art with the cited references before him would be motivated to make applicants' claimed compounds due to the functional similarity of various hydrocarbons substituents, particularly the benzoxy and alkyloxy substituents, and because all of the cited references teach diagnostic complexes of DTPA with Gd. Gries et al. provides evidence of this equivalence and it would not be beyond reasonable experimentation for the ordinarily skilled artisan to make such a modification of the Berg et al. compounds in the absence of unexpected results.

Applicants have indicated in the prior interview that unexpected results can be established but without such evidence in the record, the examiner's position is maintained. Differences between the prior art and applicants' claims alone are inadequate to establish nonobviousness; the differences must be statistically significant, unexpected and of practical significance. See, for example, In re Merck & Co. Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Freeman, 474 F.2d 1318, 177 USPQ 139 (CCPA 1973). Further, argument of counsel cannot take the place of evidence in the record. Meitzer v. Mindick, 549 F.2d 775, 782, 193 USPQ 17, 22 (CCPA), cert. denied, 434 U.S. 854 (1977).

Applicants also argue that the Ex parte Koster decision is inapplicable to the present case because it does not make a per se ruling that in all compounds, alkyl and phenyl groups are considered equivalent. This argument is also without merit because the citation of Ex parte Koster was made to provide further support to the examiner's position outlined above. Applicants point about combining Berg et al. compounds and Koster compounds is irrelevant to the discussion and is contrary to the examiner's rejection which used the legal rule of Ex parte Koster to show that case precedent has upheld rejections which turn on the question of equivalence between alkyl and aryl moieties. Although the rejection of Berg et al. in view of Gries et al. turns on the equivalence of alkoxy and benzoxy substituents, the Koster decision is believed to be applicable and relevant in the absence of unexpected results to the contrary.

With respect to the rejection over Gries et al. in view of Lauffer et al., applicants in the amendment of 9/1/95 had cancelled claims 33-35 making the rejection moot. Subsequently, applicants have added claims 41-43 and argued the rejection which would apply to these claims in the amendment of 9/19/95. This argument is also found unpersuasive in the absence of unexpected results to the contrary. Applicants argue that the teachings of the patent are generic and that the compounds disclosed in column 7, line 63-column 8, line 10 teach a combination of aryl and aliphatic groups rather than a single phenyl group. These arguments, however, are not convincing because a person of ordinary skill in the art would be motivated to attach a single phenyl group for stearic considerations and based on the teachings of the cited references would have been enabled to synthesize the claimed compounds in order to achieve the lipophilicity discussed in Lauffer et al.

9. The references cited on PTO-892 are pertinent to applicants' disclosure and are cumulative to the references cited above.

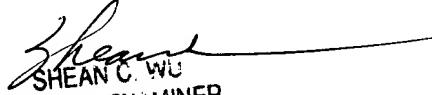
10. Applicants' amendments necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lara Chapman whose telephone number is (703) 308-0450. The examiner can normally be reached on Mondays through Thursdays and alternate Fridays from 7:30 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Geist, can be reached on (703) 308-1701. The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.


SEAN C. WU
PRIMARY EXAMINER
GROUP 1200


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November 22, 1995